NDA 21-107/S-002

Glaxo Wellcome, Inc.
Attention: Mark Baumgartner
Product Director, Regulatory Affairs
Five Moore Drive
Research Triangle Park, NC 27709

AUG 11 2000

Dear Mr. Baumgartner:

Please refer to your supplemental new drug application dated July 17, 2000, received July 18, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lotronex™ (alosetron hydrochloride) Tablets.

We also refer to the our correspondence dated August 4, 2000, in which we notified GlaxoWellcome that Pursuant to 21 C.F.R. Part 208, and based on information from post-marketing experience, FDA has determined that Lotronex™ (alosetron hydrochloride) poses a serious and significant public health concern requiring distribution of a Medication Guide.

We acknowledge receipt of your submissions dated July 18, 28, August 09, 10, and 11, 2000.

This supplemental new drug application provides for changes to the approved labeling, which includes changes to the package insert text and the immediate carton and container labels. In addition, your submission includes proposals for a new Patient Medication Guide, as well as "Dear HealthCare Practitioner" and "Dear Pharmacist" letters.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. In addition, we concur with your proposed "Dear HealthCare Practitioner" and "Dear Pharmacist" letters. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted August 11, 2000, Patient Medication Guide submitted August 11, 2000, immediate container and carton labels submitted August 10, 2000).

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format NDAs* (Januaty. 1999). For administrative purposes, this submission should be designated "FPL for approved for

supplement NDA 21-107/S-002." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MED WATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 3l4.80 and 314.81.

If you have any questions, call Paul E. Levine, Jr., R.Ph., Regulatory Project Manager, at (301) 827-7310.

Sincerely,

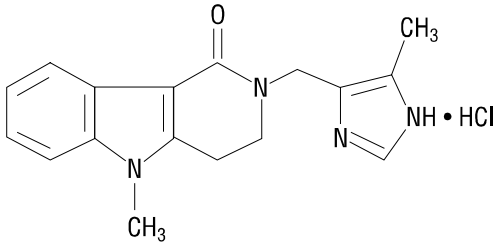
Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

PRODUCT INFORMATION

LOTRONEX®

(alosetron hydrochloride) Tablets

DESCRIPTION: The active ingredient in LOTRONEX Tablets is alosetron hydrochloride (HCl), a potent and selective antagonist of the serotonin 5-HT3 receptor type. Chemically, alosetron is designated as 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one, monohydrochloride. Alosetron is achiral and has the empirical formula: $C_{17}H_{18}N_4O$•HCl, representing a molecular weight of 330.8. Alosetron is a white to beige solid that has a solubility of 61 mg/mL in water, 42 mg/mL in 0.1M hydrochloric acid, 0.3 mg/mL in pH 6 phosphate buffer, and <0.1 mg/mL in pH 8 phosphate buffer. The chemical structure of alosetron is:



LOTRONEX Tablets for oral administration contain 1.124 mg alosetron HCl equivalent to 1 mg of alosetron. Each tablet also contains the inactive ingredients lactose (anhydrous), magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The blue film-coat contains hydroxypropyl methylcellulose, titanium dioxide, triacetin, and indigo carmine.

CLINICAL PHARMACOLOGY:

Pharmacodynamics: ***Mechanism of Action:*** Alosetron is a potent and selective 5-HT3 receptor antagonist. 5-HT3 receptors are nonselective cation channels that are extensively distributed on enteric neurons in the human gastrointestinal tract, as well as other peripheral and central locations. Activation of these channels and the resulting neuronal depolarization affect the regulation of visceral pain, colonic transit and gastrointestinal secretions, processes that relate to the pathophysiology of irritable bowel syndrome (IBS). 5-HT3 receptor antagonists such as alosetron inhibit activation of non-selective cation channels which results in the modulation of the enteric nervous system.

The cause of IBS is unknown. IBS is characterized by visceral hypersensitivity and hyperactivity of the gastrointestinal tract, which lead to abnormal sensations of pain and motor activity. Following distention of the rectum, IBS patients exhibit pain and discomfort at lower volumes than healthy volunteers. Following such distention, alosetron reduced pain and exaggerated motor responses, possibly due to blockade of 5-HT3 receptors.

In healthy volunteers and IBS patients, alosetron (2 mg orally, twice daily for 8 days) increased colonic transit time without affecting orocecal transit time. In healthy volunteers, alosetron also increased basal jejunal water and sodium absorption after a single 4-mg dose. In IBS patients, multiple oral doses of alosetron (4 mg twice daily for 6.5 days) significantly increased colonic compliance.

Single oral doses of alosetron administered to healthy men produced a dose-dependant reduction in the flare response seen after intradermal injection of serotonin. Urinary 6-β-hydroxycortisol excretion decreased by 52% in elderly subjects after 27.5 days of alosetron 2 mg orally twice daily. This decrease was not statistically significant. In another study utilizing alosetron 1 mg orally twice daily for 4 days, there was a significant decrease in urinary 6-β-hydroxycortisol excretion. However, there was no change in the ratio of 6-β-hydroxycortisol to cortisol, indicating a possible decrease in cortisol production. The clinical significance of these findings is unknown.

Pharmacokinetics: The pharmacokinetics of alosetron have been studied after single oral doses ranging from 0.05 mg to 16 mg in healthy men. The pharmacokinetics of alosetron have also been evaluated in healthy women and men and in patients with IBS after repeated oral doses ranging from 1 mg twice daily to 8 mg twice daily.

Absorption: Alosetron is rapidly absorbed after oral administration with a mean absolute bioavailability of approximately 50 to 60% (approximate range 30 to >90%). After administration of radiolabeled alosetron, only 1% of the dose was recovered in the feces as unchanged drug. Following oral administration of a 1 mg alosetron dose to young men, a peak plasma concentration of approximately 5 ng/mL occurs at 1 hour. In young women, the mean peak plasma concentration is approximately 9 ng/mL, with a similar time to peak.

***Food Effects*:** Alosetron absorption is decreased by approximately 25% by co-administration with food, with a mean delay in time to peak concentration of 15 minutes (see DOSAGE AND ADMINISTRATION).

Distribution: Alosetron demonstrates a volume of distribution of approximately 65 to 95 L. Plasma protein binding is 82% over a concentration range of 20 to 4000 ng/mL.

Metabolism and Elimination: Plasma concentrations of alosetron increase proportionately with increasing single oral doses up to 8 mg and more than proportionately at a single oral dose of 16 mg. Twice-daily oral dosing of alosetron does not result in accumulation. The terminal elimination half-life of alosetron is approximately 1.5 hours (plasma clearance is approximately 600 mL/min). Population pharmacokinetic analysis in IBS patients confirmed that alosetron clearance is minimally influenced by doses up to 8 mg.

Renal elimination of unchanged alosetron accounts for only 6% of the dose. Renal clearance is approximately 94 mL/min.

Alosetron is extensively metabolized in humans. The biological activity of these metabolites is unknown. A mass balance study was performed utilizing an orally administered dose of unlabeled and ^{14}C-labeled alosetron. This study indicates that on a molar basis, alosetron metabolites reach additive peak plasma concentrations 9-fold greater than alosetron and that the additive metabolite AUCs are 13-fold greater than alosetron's AUC. Plasma radioactivity declined with a half-life 2-fold longer than that of alosetron, indicating the presence of circulating metabolites. Approximately 73% of the radiolabeled dose was recovered in urine with another 24% of the dose recovered in feces. Only 7% of the dose was recovered as unchanged drug. At least 13 metabolites have been detected in urine. The predominant product in urine was a 6-hydroxy metabolite (15% of the dose). This metabolite was secondarily metabolized to a glucuronide that was also present in urine (14% of the dose). Smaller amounts of the 6-hydroxy metabolite and the 6-O-glucuronide also appear to be present in feces. A bis-oxidized dicarbonyl accounted for 14% of the dose and its monocarbonyl precursor accounted for another 4% in urine and 6% in feces. No other urinary metabolite accounted for more than 4% of the dose. Glucuronide or sulfate conjugates of unchanged alosetron were not detected in urine.

In studies of Japanese men, an N-desmethyl metabolite was found circulating in plasma in all subjects and accounted for up to 30% of the dose in one subject when alosetron was administered with food. The clinical significance of this finding is unknown.

Alosetron is metabolized by human microsomal cytochrome P450 (CYP), shown in vitro to involve enzymes 2C9 (30%), 3A4 (18%), and 1A2 (10%). Non-CYP mediated Phase I metabolic conversion also contributes to an extent of about 11% (see PRECAUTIONS: Drug Interactions).

Population Subgroups: ***Age:*** In some studies in healthy men or women, plasma concentrations were elevated by approximately 40% in individuals 65 years and older compared to young adults. However, this effect was not consistently observed in men (see PRECAUTIONS: Geriatric Use and DOSAGE AND ADMINISTRATION: Geriatric Patients).

Gender: Plasma concentrations are 30% to 50% lower and less variable in men compared to women given the same oral dose. Population pharmacokinetic analysis in IBS patients confirmed that alosetron concentrations were influenced by gender (27% lower in men).

Reduced Hepatic Function: No pharmacokinetic data are available in this patient group (see PRECAUTIONS: Hepatic Insufficiency and DOSAGE AND ADMINISTRATION: Patients with Hepatic Impairment).

Reduced Renal Function: Renal impairment (creatinine clearance 4 to 56 mL/min) has no effect on the renal elimination of alosetron due to the minor contribution of this pathway to elimination. The effect of renal impairment on metabolite kinetics and the effect of end-stage renal disease have not been assessed (see DOSAGE AND ADMINISTRATION: Patients with Renal Impairment).

CLINICAL TRIALS: Two 12-week treatment, multi-center, double-blind, placebo-controlled, dose-ranging studies were conducted to determine the dosage of oral LOTRONEX for subsequent evaluation in efficacy studies.

In women, of the doses studied, 1 mg of LOTRONEX twice daily was significantly more effective than placebo in providing relief of IBS pain and discomfort, decreasing the proportion of days with urgency, decreasing stool frequency, and producing firmer stools. Efficacy in men, as assessed by producing adequate relief of IBS pain and discomfort, was not demonstrated at any dose of LOTRONEX.

The efficacy and safety of 1 mg of oral LOTRONEX twice daily for 12 weeks was studied in two US multi-center, double-blind, placebo-controlled trials of identical design (Studies 1 and 2) in non-constipated women with IBS meeting the Rome Criteria[1] for at least 6 months. For enrollment into the studies, patients were required to meet entry pain and stool consistency criteria. An average pain score of at least mild pain, as collected during a 2-week screening period, was required. Women with severe pain were excluded. An entry stool consistency requirement was also incorporated to target women whose predominant bowel symptom was diarrhea or in which diarrhea was a prominent feature in their alternating pattern. Women with a history of severe constipation were excluded. Men were not studied.

The primary efficacy measure in these studies was the woman's weekly assessment of adequate relief of IBS pain and discomfort. Key secondary measures included percentage of days with urgency and daily assessment of stool frequency and consistency. Study 1 enrolled 647 women (71% diarrhea-predominant, 28% alternating between diarrhea and constipation, and 1% constipation-predominant) while Study 2 enrolled 626 women (71% diarrhea-predominant, 27% alternating between diarrhea and constipation, and 2% constipation-predominant). At entry into the studies, most women reported mild to moderate pain intensity and stool consistency of formed to loose.

In both trials, LOTRONEX 1 mg administered twice daily was significantly more effective than placebo in providing relief of IBS pain and discomfort.

In both Study 1 and Study 2, the beneficial effect on IBS pain and discomfort was demonstrated only in women with diarrhea-predominant IBS. Data in Figures 1 and 2 are presented for this subgroup. In Study 1, significantly more women reported relief of their abdominal pain and discomfort within 1 week of starting alosetron therapy than those who received placebo (Figure 1). In Study 2, this treatment effect was observed

within 4 weeks (Figure 2). Once attained, significant treatment effect persisted throughout the remainder of the treatment period. Upon discontinuing LOTRONEX, symptoms returned. Within one week after discontinuing therapy, there was no difference between placebo and alosetron-treated women.

Figure 1: Percentage of Women (Diarrhea-Predominant) Reporting Relief of IBS Pain and Discomfort in Study 1

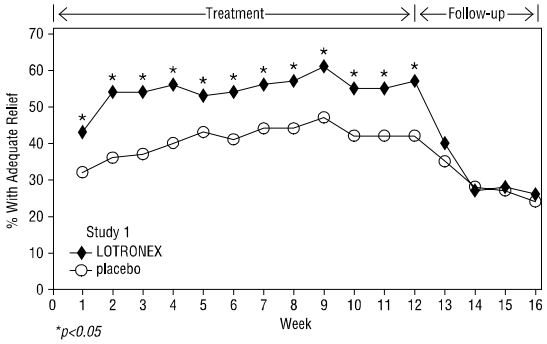
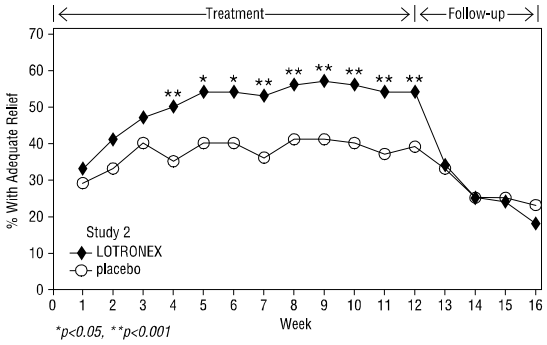


Figure 2: Percentage of Women (Diarrhea-Predominant) Reporting Relief of IBS Pain and Discomfort in Study 2



In each study, women who received LOTRONEX reported a significant decrease in the percentage of days with urgency as compared to those who received placebo. Treatment with LOTRONEX also resulted in firmer stools and a significant decrease in stool frequency. Significant improvement of these symptoms occurred within the first week of treatment and persisted throughout the 12 weeks of therapy. Upon discontinuance of treatment these symptoms returned. Within one week after discontinuing therapy, there was no difference between placebo and alosetron-treated patients. The efficacy of LOTRONEX for treatment longer than 12 weeks has not been established.

INDICATIONS AND USAGE: LOTRONEX is indicated for the treatment of women with diarrhea-predominant irritable bowel syndrome (IBS). Diarrhea-predominant IBS is characterized by at least 3 months of recurrent or continuous symptoms of abdominal pain or discomfort with either urgency, an increase in frequency of stool, or diarrhea not attributable to organic disease (see APPENDIX).

In men, the safety and effectiveness of LOTRONEX have not been established.

CONTRAINDICATIONS:

LOTRONEX should not be **initiated** in patients with constipation (fewer than three bowel movements a

week and/or hard or lumpy stools and/or straining during a bowel movement) (see WARNINGS).

LOTRONEX is contraindicated in patients:

- With a history of chronic or severe constipation or with a history of sequelae from constipation.
- With a history of intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforation, and/or adhesions.
- With a history of ischemic colitis.
- With current or a history of Crohn's Disease or ulcerative colitis.
- With active diverticulitis.
- With known hypersensitivity to any component of the product.

WARNINGS:

Constipation:

Serious complications of constipation, including obstruction, perforation, impaction, toxic megacolon, and secondary ischemia, have been infrequently reported in association with administration of LOTRONEX. In some cases these complications have required intestinal surgery, including colectomy.

LOTRONEX should not be prescribed for patients presenting with constipation or those with a history of chronic or severe constipation, history of sequelae from constipation, or history of intestinal obstruction, stricture, toxic megacolon, and/or gastrointestinal perforation, or adhesions.

LOTRONEX treatment should be discontinued immediately in patients with severe constipation. Treatment with LOTRONEX should not be resumed in patients who develop severe constipation while receiving the drug (see CONTRAINDICATIONS). Patients with non-severe constipation should be closely monitored. Non-severe constipation can be managed with an interruption of therapy or usual care, including laxatives. If constipation does not resolve within 4 days with these measures, treatment with LOTRONEX should be discontinued and not resumed.

Ischemic Colitis:

Ischemic colitis has been reported in patients receiving LOTRONEX in clinical trials as well as during marketed use of the drug. In clinical trials, the frequency of ischemic colitis in women receiving LOTRONEX was approximately 1 in 700 patients.

LOTRONEX should be discontinued immediately in patients with signs of ischemic colitis such as sudden onset of rectal bleeding, bloody diarrhea, or new or sudden worsening abdominal pain. Because ischemic colitis can be life-threatening, patients with signs or symptoms of ischemic colitis should be evaluated promptly and have appropriate diagnostic testing performed. Treatment with LOTRONEX should not be resumed in patients who have developed ischemic colitis.

PRECAUTIONS:

Information for Patients: Before prescribing LOTRONEX, physicians should discuss with patients how troublesome their IBS symptoms are, the possible benefits of LOTRONEX, and its possible side effects. Patients should be instructed to read the Medication Guide supplied with their prescription for LOTRONEX. The complete text of the Medication Guide is reprinted at the end of this document.

The Medication Guide informs women that LOTRONEX has been associated with ischemic colitis and serious complications of constipation. Both of these conditions are serious and may need hospitalization or surgery. Patients should be told to stop using LOTRONEX and call their doctor right away if any of the following occur:

- severe constipation
- existing constipation that becomes bothersome, worse, or is associated with increased abdominal

discomfort
- new or worsening abdominal pain
- bloody diarrhea or blood in the stool

Patients should be instructed to call their doctor right away if they develop constipation.

Drug Interactions: In vitro human liver microsome studies and an in vivo metabolic probe study demonstrated that alosetron did not inhibit CYP enzymes 2D6, 3A4, 2C9, or 2C19. In vitro, at total drug concentrations 27-fold higher than peak plasma concentrations observed with the 1-mg dosage, alosetron inhibited CYP enzymes 1A2 (60%) and 2E1 (50%). In an in vivo metabolic probe study, alosetron did not inhibit CYP2E1 but did produce 30% inhibition of both CYP1A2 and N-acetyltransferase. Although not studied with alosetron, inhibition of N-acetyltransferase may have clinically relevant consequences for drugs such as isoniazid, procainamide, and hydralazine. The effect on CYP1A2 was explored further in a clinical interaction study with theophylline and no effect on metabolism was observed. Another study showed that alosetron had no clinically significant effect on plasma concentrations of the oral contraceptive agents ethinyl estradiol and levonorgestrel (CYP3A4 substrates). A clinical interaction study was also conducted with alosetron and the CYP3A4 substrate cisapride. No significant effects on cisapride metabolism or QT interval were noted. The effect of alosetron on monoamine oxidases and on intestinal first pass secondary to high intraluminal concentrations have not been examined. Based on the above data from in vitro and in vivo studies, it is unlikely that alosetron will inhibit the hepatic metabolic clearance of drugs metabolized by the major CYP enzyme 3A4, as well as the CYP enzymes 2D6, 2C9, 2C19, 2E1, or 1A2.

Alosetron does not appear to induce the major cytochrome P450 (CYP) drug metabolizing enzyme 3A. Alosetron also does not appear to induce CYP enzymes 2E1 or 2C19. It is not known whether alosetron might induce other enzymes.

Because alosetron is metabolized by a variety of hepatic CYP drug-metabolizing enzymes, inducers or inhibitors of these enzymes may change the clearance of alosetron. The effect of induction or inhibition of individual pathways on metabolite kinetics and pharmacodynamic consequences has not been examined.

Hepatic Insufficiency: Due to the extensive hepatic metabolism and first pass metabolism of alosetron and metabolites, increased exposure to alosetron is likely to occur in patients with hepatic insufficiency.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In 2-year oral studies, alosetron was not carcinogenic in mice at doses up to 30 mg/kg/day or in rats at doses up to 40 mg/kg/day. These doses are, respectively, about 60 to 160 times the recommended human dose of alosetron of 2 mg/day (1 mg twice daily) based on body surface area. Alosetron was not genotoxic in the Ames tests, the mouse lymphoma cell ($L5178Y/TK^{\pm}$) forward gene mutation test, the human lymphocyte chromosome aberration test, the ex vivo rat hepatocyte unscheduled DNA synthesis (UDS) test, or the in vivo rat micronucleus test for mutagenicity. Alosetron at oral doses up to 40 mg/kg/day (about 160 times the recommended daily human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male or female rats.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category B. Reproduction studies have been performed in rats at doses up to 40 mg/kg/day (about 160 times the recommended human dose based on body surface area) and rabbits at oral doses up to 30 mg/kg/day (about 240 times the recommended daily human dose based on body surface area). These studies have revealed no evidence of impaired fertility or harm to the fetus due to alosetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, LOTRONEX should be used during pregnancy only if clearly needed.

Nursing Mothers: Alosetron and/or metabolites of alosetron are excreted in the breast milk of lactating rats. It is not known whether alosetron is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when LOTRONEX is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.
Geriatric Use: Of all patients who received at least one dose of alosetron in premarketing studies, 211 were 65 years of age and over and 39 were 75 years of age and over. The safety profile of LOTRONEX was similar in older and younger patients.

In 2 placebo-controlled IBS safety and efficacy trials (Studies 1 and 2), 60 patients 65 years of age and over and 14 patients 75 years of age and over received 1-mg oral doses of LOTRONEX twice daily for up to 12 weeks. In both studies, subgroup analyses showed no evidence of differential treatment effects across the age categories assessed. Other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out (see CLINICAL PHARMACOLOGY: Population Subgroups: Age).

ADVERSE REACTIONS: In two large, placebo-controlled clinical trials conducted in the US (Studies 1 and 2), women (18 years of age and older) were treated with 1 mg of LOTRONEX twice daily for up to 12 weeks. The adverse events in Table 1 were reported in 1% or more of patients who received LOTRONEX and occurred more frequently on LOTRONEX than on placebo. A statistically significant difference was observed for constipation in patients treated with LOTRONEX compared to placebo ($p<0.0001$).

Table 1: Adverse Events Reported in ≥1% of Female Patients and More Frequently on LOTRONEX 1 mg B.I.D. than Placebo (Studies 1 and 2)

Body System Adverse Event	LOTRONEX (N = 632)	Placebo (N = 637)
Cardiovascular		
Hypertension	2%	<1%
Ear, Nose, and Throat		
Allergic rhinitis	2%	<1%
Throat and tonsil discomfort and pain	1%	<1%
Bacterial ear, nose, and throat infections	1%	<1%
Gastrointestinal		
Constipation	28%	5%
Nausea	7%	6%
Gastrointestinal discomfort and pain	5%	4%
Abdominal discomfort and pain	5%	3%
Gastrointestinal gaseous symptoms	3%	2%
Viral gastrointestinal infections	3%	2%
Dyspeptic symptoms	3%	1%
Abdominal distention	2%	<1%
Hemorrhoids	2%	<1%
Neurology		
Sleep disorders	3%	2%
Psychiatry		
Depressive disorders	2%	1%

Gastrointestinal: Constipation is a frequent and dose-related side effect of treatment with LOTRONEX (see WARNINGS). In clinical studies, constipation was reported in 25% to 30% of patients treated with LOTRONEX 1 mg twice daily for up to 12 weeks (n = 702). This effect was statistically significant compared to placebo ($p<0.0001$). Ten percent (10%) of patients treated with LOTRONEX withdrew from the studies due to constipation. Of the patients reporting constipation, 75% reported a single episode with the mean time to constipation onset of about 3 weeks. Occurrences of constipation in clinical trials were generally mild to moderate in intensity, transient in nature, and resolved either spontaneously with continued treatment or with an interruption of treatment. However, serious complications of constipation have been infrequently observed in post-marketing experience (see WARNINGS). In studies 1 and 2, 9% of patients treated with LOTRONEX reported constipation and 4 consecutive days with no bowel movement; by protocol, therapy was withheld for 1 to 4 days. Following interruption of treatment, 88% of the affected patients resumed bowel movements within the 4-day period and were able to re-initiate treatment with LOTRONEX.

Hepatic: A similar incidence in elevation of ALT (>3-fold) was seen in patients receiving LOTRONEX or placebo (0.5% vs 0.4%) in studies of 12 weeks' and 12 months' duration. A single case of hepatitis (elevated ALT, AST, alkaline phosphatase, and bilirubin) without jaundice was reported in a 12-week study. A causal association with LOTRONEX has not been established.

Long-Term Safety: The pattern and frequency of adverse events in a long-term, placebo-controlled safety study in which women with IBS (n = 473) were treated with LOTRONEX 1 mg twice daily for up to 12 months were essentially the same as observed in 12-week safety and effectiveness trials. There were no reports of acute colitis in these alosetron-treated women.

Other Events Observed During the Premarketing Evaluation of LOTRONEX: During its premarketing assessment, multiple and single doses of LOTRONEX were administered resulting in 2574 patient exposures in 46 completed clinical studies. The conditions, dosages, and duration of exposure to LOTRONEX varied between trials, and the studies included healthy male and female volunteers as well as male and female patients with IBS.

In the listing that follows, reported adverse events were classified using a standardized coding dictionary. Only those events that an investigator believed were possibly related to alosetron, occurred in at least 2 patients, and occurred at a greater frequency during treatment with LOTRONEX than during placebo administration are presented. Serious adverse events occurring in at least 1 patient for which an investigator believed there was reasonable possibility that the event was related to alosetron treatment and which occurred at a greater frequency in LOTRONEX than placebo-treated patients are also presented.

In the following listing, events are categorized by body system. Within each body system, events are presented in descending order of frequency. The following definitions are used: *Infrequent* adverse events are those occurring on one or more occasion in 1/100 to 1/1000 patients; *Rare* adverse events are those occurring on one or more occasion in fewer than 1/1000 patients.

Although the events reported occurred during treatment with LOTRONEX, they were not necessarily caused by it.

Cardiovascular - Infrequent: Arrhythmias.

Drug Interaction, Overdose and Trauma - Rare: Contusions and hematomas.

Ear, Nose, and Throat - Infrequent: Nasal signs and symptoms. ***Rare:*** Ear signs and symptoms.

Eyes - Rare: Photophobia.

Gastrointestinal - Infrequent: Ischemic colitis (see WARNINGS). ***Rare:*** proctitis.

Hepatobiliary Tract and Pancreas - Infrequent: Abnormal bilirubin levels.

Lower Respiratory - Infrequent: Breathing disorders. ***Rare:*** Cough.

Neurological - Rare: Sedation and abnormal dreams.

Non-site Specific - Rare: Allergies, allergic reactions, unusual odors and taste.

Psychiatry - Infrequent: Anxiety.

Reproduction - Infrequent: Menstrual disorders. ***Rare:*** Sexual function disorders.

Skin - Rare: Acne and folliculitis.

Urology - Rare: Urinary infections, polyuria, and diuresis.

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during use of LOTRONEX in clinical practice and from noncontrolled investigational use. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to LOTRONEX.

Gastrointestinal: Constipation that in rare cases resulted in severe sequelae (e.g., impaction, obstruction, perforation, ulceration), and ischemic colitis (see WARNINGS).

DRUG ABUSE AND DEPENDENCE: LOTRONEX has no known potential for abuse or dependence.

OVERDOSAGE: There is no specific antidote for overdose of LOTRONEX. Patients should be managed with appropriate supportive therapy. Individual oral doses as large as 16 mg have been administered in clinical

studies without significant adverse events. This dose is 8 times higher than the recommended total daily dose. Inhibition of the metabolic elimination and reduced first pass of other drugs might occur with overdoses of alosetron (see PRECAUTIONS: Drug Interactions). Single oral doses of LOTRONEX at 15 mg/kg in female mice and 60 mg/kg in female rats (30 and 240 times, respectively, the recommended human dose based on body surface area) were lethal. Symptoms of acute toxicity were labored respiration, subdued behavior, ataxia, tremors, and convulsions.

DOSAGE AND ADMINISTRATION:

Usual Dose in Adults: The recommended adult dosage of LOTRONEX is 1 mg taken orally twice daily with or without food.

LOTRONEX should be discontinued immediately in patients with severe constipation. Treatment with LOTRONEX should not be resumed in patients who develop severe constipation while receiving the drug. Patients with non-severe constipation should be closely monitored. Non-severe constipation can be managed with an interruption of therapy or usual care, including laxatives. If constipation does not resolve within 4 days with these measures, treatment with LOTRONEX should be discontinued and not resumed (see WARNINGS, CONTRAINDICATIONS, and ADVERSE REACTIONS: Gastrointestinal).

LOTRONEX should be discontinued in patients who have not had improvement of IBS symptoms after four weeks of treatment.

Pediatric Patients: No studies have been conducted in patients less than 18 years of age (see PRECAUTIONS: Pediatric Use).

Geriatric Patients: No dosage adjustment is recommended for elderly patients (65 years of age and older) (see CLINICAL PHARMACOLOGY: Population Subgroups: Age and PRECAUTIONS: Geriatric Use).

Patients with Renal Impairment: No dosage adjustment is recommended for patients with renal impairment (creatinine clearance 4 to 56 mL/min) (see CLINICAL PHARMACOLOGY: Reduced Renal Function).

Patients with Hepatic Impairment: No studies have been conducted in patients with hepatic impairment (see PRECAUTIONS: Hepatic Insufficiency and CLINICAL PHARMACOLOGY: Population Subgroups: Reduced Hepatic Function).

HOW SUPPLIED: LOTRONEX Tablets, 1 mg (1.124 mg alosetron HCl equivalent to 1 mg alosetron), are blue, oval, film-coated tablets debossed with GX CT1 on one face in bottles of 60 (NDC 0173-0690-00) with child-resistant closures .

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

APPENDIX (see INDICATIONS AND USAGE):

Diagnostic Criteria for Diarrhea-Predominant Irritable Bowel Syndrome (IBS)[2]
At least 12 weeks or more, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two out of three features: (1) Relieved with defecation, and/or (2) Onset associated with increased frequency of stool, and/or (3) Onset associated with a loose appearance of stool and, Symptoms that Cumulatively Support the Diagnosis of Diarrhea-Predominant Irritable Bowel Syndrome: (1) Abnormal stool frequency (greater than 3 bowel movements per day), (2) Abnormal stool form (loose/watery stool), (3) Abnormal stool passage (urgency or feeling of incomplete evacuation). Above symptoms not attributable to organic disease.

REFERENCES:

1. Thompson WG, Creed F, Drossman DA, et al. Functional bowel disease and functional abdominal pain. *Gastroenterol Int*. 1992;5:75-91.
2. Adapted from Thompson WG, Longstreth GF, Drossman DA, et al. Functional bowel disorders and functional abdominal pain. *Gut.* 1999;45(Suppl.II); II:43-47.

GlaxoWellcome
Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

US Patent No. 5,360,800

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LOTRONEX® (alosetron hydrochloride) Tablets

MEDICATION GUIDE

LOTRONEX® (LOW-trah-nex) Tablets
alosetron hydrochloride

Read this information carefully before you start taking LOTRONEX Tablets. Read the information you get with LOTRONEX each time you refill your prescription. There may be new information. This information does not take the place of talking with your doctor.

What is the most important information I should know about LOTRONEX?
LOTRONEX is used to help women who have irritable bowel syndrome (IBS) with diarrhea as their main symptom (diarrhea-predominant IBS). **Women who have constipation as their main IBS symptom should not use LOTRONEX.** LOTRONEX has not been shown to help men.

IBS generally does not result in a need for bowel surgery (operation). A few patients taking LOTRONEX can develop intestinal side effects serious enough to need hospitalization and possibly surgery. **Before starting LOTRONEX, discuss with your doctor how troublesome your IBS symptoms are, the possible benefits of LOTRONEX, and its possible side effects to decide if LOTRONEX is right for you.**

Possible serious side effects of LOTRONEX include:

1. **Constipation**
   LOTRONEX may result in constipation that infrequently may be serious enough to block movement of stools through the intestines. In a few women, this may lead to hospitalization and possibly surgery.
   - **Do not start taking LOTRONEX if you are constipated.**
   - **If you get constipated while taking LOTRONEX call your doctor right away. If you develop any of the following symptoms while waiting to talk to your doctor, stop taking LOTRONEX:**
     - **severe constipation**
     - **worsening or bothersome constipation with increased abdominal discomfort**

   Do not start taking LOTRONEX again until you talk to your doctor.

2. **Ischemic colitis**
   Some patients (about 1 in 700) developed ischemic colitis while using LOTRONEX. Ischemic colitis is a serious condition caused by reduced blood flow to the intestines. This condition may need hospitalization and possibly surgery. **Stop using LOTRONEX and call your doctor right away** if you have any of these signs of ischemic colitis:
   - new or worsening abdominal (lower stomach area) pain
   - bloody diarrhea or blood in the stool (bowel movements)

What is LOTRONEX?
LOTRONEX is a prescription medicine used to treat IBS in women who have diarrhea as their main symptom (diarrhea-predominant). LOTRONEX has not been shown to help men with IBS.

IBS is also called irritable colon and spastic colon. IBS causes lower abdominal (stomach) pain and discomfort, urgency (a sudden need to have a bowel movement), and irregular bowel habits, such as diarrhea or constipation. It is not clear why people develop IBS. Some scientists think IBS is caused by an overreaction to a body chemical called serotonin. This may cause patients' intestines to be overactive. IBS

can be constipation-predominant, diarrhea-predominant, or can involve constipation and diarrhea. LOTRONEX is only for women with diarrhea-predominant IBS.

LOTRONEX does not help everyone. For those who get relief, LOTRONEX helps reduce IBS-related lower abdominal pain, abdominal discomfort, urgency and diarrhea. You may get relief of some or all of your symptoms after 1 to 4 weeks of use. If LOTRONEX does not reduce your symptoms after 4 weeks, stop using it and tell your doctor.

LOTRONEX does not cure IBS. When you stop taking LOTRONEX, your IBS symptoms will probably return within 1 week.

Who should not take LOTRONEX?
LOTRONEX is not right for everyone. It is only for women with troublesome diarrhea-predominant IBS.

1. Do not **start** taking LOTRONEX if you are constipated
2. Do not **ever** take LOTRONEX if you
   - are constipated most of the time
   - have ever had severe constipation or a serious problem from constipation
   - have ever had ischemic colitis
   - have ever had Crohn's Disease or ulcerative colitis
   - have active diverticulitis
   - are allergic to LOTRONEX or any of its ingredients (see list of ingredients at the end of this Medication Guide).

If you take LOTRONEX under these conditions, you increase your risk of getting serious side effects.

Tell your doctor if you are pregnant, planning to get pregnant, breast feeding, or taking or planning to take other prescription or non-prescription medicines.

How should I take LOTRONEX?
Take LOTRONEX exactly as your doctor prescribes it. You can take LOTRONEX with or without food. If you miss a dose of LOTRONEX, do not double the next dose. Wait until the next scheduled dosing time and take your normal dose.

What are the possible side effects of LOTRONEX?
Constipation is the most common side effect of LOTRONEX. A few patients may develop serious intestinal side effects. A description of these side effects, how to identify them, and what action to take if you get them, is in the first section of this Medication Guide, "What is the most important information I should know about LOTRONEX?" Refer to the information about constipation and ischemic colitis in that section.

These are not all the side effects of LOTRONEX. Your doctor or pharmacist can give you a more complete list.

General advice about prescription medicines
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you have any concerns about LOTRONEX, ask your doctor. Your doctor or pharmacist can give you information about

LOTRONEX that was written for health care professionals. Do not use LOTRONEX for a condition for which it was not prescribed. Do not share LOTRONEX with other people.

Ingredients: alosetron hydrochloride, lactose (anhydrous), magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The blue film-coat contains hydroxypropyl methylcellulose, titanium dioxide, triacetin, and indigo carmine.

This Medication Guide has been approved by the US Food and Drug Administration.

GlaxoWellcome

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